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Proposed Linking Claims

1. A polynucleotide comprising at least two repeats of a hypoxia response element (HRE) wherein the hypoxia-inducible factor (HIF) consensus binding sites within each of the two repeats are separated by a spacer of at least 20 contiguous nucleotides.

2. The polynucleotide of claim 1, wherein the HRE repeats are optionally linked to a viral promoter.

3. The polynucleotide of claim 1, wherein the space comprises a nucleotide sequence of SEQ ID NO: 10 or 11.

4. The polynucleotide of claim 2, wherein the promoter is an SV40 promoter or an MLV promoter.

5. The polynucleotide of claim 2, comprising at least four HRE repeats linked to the promoter, where at least two repeats are positioned upstream (5') of the promoter and at least two repeats are positioned downstream (3') of the promoter.

6. The polynucleotide of claim 2, comrising at least three HRE repeats, wherein the HREs are phosphoglycerate kinase HREs, and wherein the promoter is an SV40 promoter or an MLV promoter.

7. The polynucleotide of claim 6, comprising at least six HRE repeats linked to the promoter, where at least three repeats are positioned upstream (5') of the promoter and at least three repeats are positioned downstream (3') of the promoter.

8. The polynucleotide of claim 1, wherein the HRE repeats are direct repeats.

9. The polynucleotide of claim 1, wherein the HRE repeats comprise a nucleotide sequence of SEQ ID NO: 1 or 2.

10. The polynucleotide of claim 1, comprising the nucleic acid sequence of SEQ ID NO:9.

11. The polynucleotide of claim 6, comprising the nucleic acid sequence of SEQ ID NO:3, 4, or 5.

12. The polynucleotide of claim 2, operably linked to a nucleic acid of interest (NOI) such that the polynuclotide directs expression of the NOI in a host cell.

13. The polynucleotide of claim 12, wherein the NOI encodes HIF-1.

14. The polynucleotide of claim 13, wherein the promoter lacks a CAAT box sequence.

15. The polynucleotide of claim 12, wherein the host cell is a tumor cell.

16. The polynucleotide of claim 12, wherein the NOI encodes a therapeutic peptide.

17. The polynucleotide of claim 12, wherein the NOI encodes a cytotoxic polypeptide.

18. The polynucleotide of claim 12, wherein the NOI encodes a polypeptide capable of converting a precursor prodrug into a cytotoxic compound.

19. The polynucleotide of claim 12, wherein the NOI is a heat shock protein, a transcription factor; a metabolic enzyme, or proliferation-regulating protein.

20. The polynucleotide of claim 12, for use delivering the NOI to a mammalian cell.

21. The polynucleotide of claim 1, disposed in a nucleic acid vector.

22. The polynucleotide of claim 21, disposed in a nucleic acid viral vector.

23. The polynucleotide of claim 22, disposed in a viral vector that further comprises a nucleotide sequence selected from (i) a nucleotide sequence encoding an inhibitory RNA molecule capable of effecting the cleavage, directly or indirectly, of VHL RNA; (ii) one or more inhibitory RNA molecules that bind to and prevent VHL RNA processing and/or expression; and (iii) a nucleotide sequence encoding a polypeptide capable of inhibiting the binding of VHL to Elongin B and/or Elongin C.

24. The polynucleotide of claim 22, wherein said polypeptide is a non-functional derivative of wild type VHL.

25. The polynucleotide of claim 22, wherein the viral vector is a retroviral vector.

26. The polynucleotide of claim 22, wherein the viral vector is a adenoviral vector.

27. The polynucleotide of claim 22, wherein the viral vector is a lentiviral vector.

28. A method for the treatment of hypoxia, a disease caused by hypoxia, or a disease where hypoxia is a symptom or is other wise present, comprising administering a polynucleotide of claim 1.

29. The polynucleotide of claim 1, further comprising a pharmaceutically acceptable carrier or dilluent.

30. A method for the treatment of hypoxia, a disease caused by hypoxia, or a disease where hypoxia is a symptom or is other wise present, comprising administering a polynucleotide of claim 29.

31. A method for producing a viral strain comprising introducing the polynucleotide of claim 2 into the genome of a virus.